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Uterus transplantation—questions and answers about the procedure that is expanding the field of solid organ transplantation

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ABSTRACT

Uterus transplant is a new and rapidly evolving field of solid organ transplantation designed to help women with absolute uterine-factor infertility who desire to carry their own pregnancies. The advent of this procedure and human clinical trials of uterus transplantation have raised technical, clinical, and ethical questions. We address several questions about uterus transplantation based on available literature and the clinical experience at Baylor University Medical Center, which has the largest uterus transplant program in the United States.

KEYWORDS Allocation; complications; cost; ethics; uterus transplantation

CME

Target audience: All physicians

Learning objectives: After reading the article, the learner should be able to

1. Describe the indications for uterus transplantation and alternatives for parenthood
2. Discuss the risks of the uterus transplant and living uterus donor procedures
3. Assess arguments for and against the justification of uterus transplantation

Faculty credentials/disclosure: Anji E. Wall, MD, PhD, is an abdominal transplant surgeon and bioethicist at the Baylor Simmons Transplant Institute who does qualitative and ethics research in the field of uterus transplantation. Giuliano Testa, MD, MBA, is chief of the division of abdominal transplantation at Baylor Simmons Transplant Institute and the principal investigator of the Baylor University Medical Center uterus transplantation clinical trial. David Axelrod, MD, PhD, is an abdominal transplant surgeon and transplant research director at the University of Iowa. Liza Johannesson, MD, PhD, is the medical director of the uterus transplant program at Baylor University Medical Center and a world leader in uterus transplant research. Dr. Axelrod disclosed relationships with Care Dx, Talaris, and Specialist Direct. The other authors and the planner for this educational activity had no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by or on patients.

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Absolute uterine-factor infertility (AUFI) affects 3% to 5% of reproductive-aged infertile women worldwide and is attributed to congenital causes (e.g., Mayer-Rokitansky-Küster-Hauser syndrome) and acquired causes (e.g., previous hysterectomy).[1] Uterus transplantation (UTx) has emerged as the only treatment for women with AUFI who desire to carry their own pregnancies. The first live births after UTx from living and deceased donors occurred in 2014[2] and 2017,[3] respectively. The first live birth in the US after UTx was in 2017 at Baylor University Medical Center (BUMC).[4] To date, more than 60 UTx procedures have been reported, with at least 18 live births.[2–7] There are three active UTx programs in the United States, which make up the US Uterus Transplant Consortium: BUMC, Cleveland Clinic, and the University of Pennsylvania.[8] Given the rapid growth and clinical success of UTx, it is important for members of the medical community to be knowledgeable about this procedure. This article provides answers to several common questions asked about UTx.

UTERUS TRANSPLANTATION QUESTIONS AND ANSWERS

The following questions were posed by one of the authors (D.A.), an abdominal transplant surgeon with no experience in UTx. Answers are based on the current literature as well as the BUMC experience with UTx.

What motivates patients to undergo UTx rather than pursue adoption or surrogacy?

This is an exceedingly important question that must be answered to justify the continuation of UTx. A semistructured interview study of patients with AUFI who self-referred for UTx in the United Kingdom found that most patients preferred UTx to surrogacy due to considerations of control, cost, and the experience of gestation, and to adoption due to the desire for a biological relationship and concern about the bureaucratic challenges of adoption.[9] In a mixed-methods study of UTx applicants, the Cleveland Clinic team found that choice, control, and privacy were all motivating factors for pursuit of UTx.[10] UTx was seen as a unique option that gives women the opportunity to play an active role in their child's health and well-being as opposed to a more passive role with adoption and surrogacy.

In addition to motivation, lived experience is an essential element of UTx that must be studied. If the experiences of recipients do not meet their expectations and fulfill the motivations for UTx, then we must rethink offering this procedure. One example of this is the question about whether birth outcomes following pregnancy after UTx will be similar to non-UTx pregnancies and if, in turn, a post-UTx pregnancy will have the same perceived value as other pregnancies. BUMC reported the pregnancy experience of our first two successful UTx patients in a joint narrative that described the signs and symptoms of pregnancy such as morning sickness, cravings, nesting behavior, and fetal movement, the treatment of our UTx patients as pregnant by strangers, and the value that these two UTx recipients attributed to the pregnancy experience, which included bonding with the fetus in utero and being able to breastfeed right away.[11] Currently, BUMC is conducting a mixed-methods study of UTx recipients and their partners to elucidate both the motivations of patients who pursued UTx and their perceptions of the UTx experience. Interviews cover all of the UTx recipients, including those with failed grafts, those who have had successful pregnancies, and those still awaiting embryo transfer. This will allow us to report a wide range of perceptions regarding the UTx experience.

What surgical complications have been observed to date?

Complications have been observed in both living donors and recipients. While several centers have reported donor complications in the literature, the full scope of complications is not known because there is no worldwide working registry for UTx donors or recipients. A 2019 report of the first 45 UTx cases provides the most comprehensive overview of donor and recipient complications to date.[6] In addition to this overview, some programs have reported their single-center donor and recipient complications.[12–15]

The donor hysterectomy involves either a lower midline laparotomy or a minimally invasive approach with dissection of the uterus along with its vascular supply, including the bilateral uterine arteries and inferior and/or superior uterine veins.[15,16] For the minimally invasive donor operations, the graft can be removed through a laparotomy incision or transvaginally and is flushed immediately through the bilateral uterine arteries on the backtable *(Figure 1)*.[16]

In the BUMC trial, 13 open and 5 robotic donor hysterectomies were performed. Open donors experienced the following complications: blood loss anemia (1), gluteal claudication (1), urinary tract infection (7), depression (1), fecal impaction (1), *Clostridium difficile* colitis (1), and vaginal cuff dehiscence (1).[14] Nine of the 13 open living donors also reported dyspareunia upon the resumption of sexual activity. Robotic donor complications from the BUMC series included hydronephrosis requiring ureteral stent placement

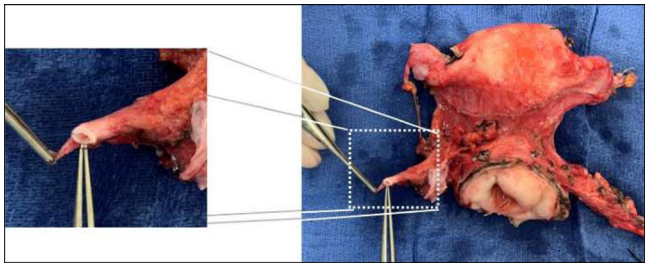

Figure 1. Backtable photograph of a uterine graft after dissection. The magnified box on the left shows the right uterine artery orifice.

and a bilateral ureteral leak secondary to thermal injury treated with ureteral stent placement.[15] Open donor complications reported by the team in Sweden included wound infection (1), ureteric vaginal fistula requiring surgical revision (1), thigh sensory impairment (1), and nocturia (1).[12] Open donor complications reported by the Czech team included a ureter laceration recognized and repaired intraoperatively (1), bladder hypotonia (1), and climacteric sexual symptoms (2).[13] No donor complications were reported in the German and Indian clinical trials.[16,17] However, one donor graft from the German trial was not usable due to inability to flush.[17]

The recipient operation is performed through a lower midline laparotomy. The bilateral donor uterine arteries as well as at least one venous outflow (superior and inferior uterine veins) per side are anastomosed to the recipient external iliac vessels in an end-to-side fashion and then an end-to-end vaginal anastomosis is performed *(Figure 2)*. Recipient complications can be related to the surgical procedures, immunosuppression, infection, rejection, or pregnancy. In the BUMC trial,[18] recipient complications included 6 early graft failures (3 due to thrombosis, 2 due to graft selection, and 1 due to ischemia secondary to hemorrhagic shock), 2 bladder injuries (recognized and repaired intraoperatively), calcineurin inhibitor (CNI)-related nephrotoxicity (2), and rejection (7 episodes, all treated and resolved with steroids). Complications of the 9 recipients in the Czech trial included urinary tract infection (2), graft thrombosis (2), vesicovaginal fistula (1), vaginal stricture (1), and herpes simplex virus infection requiring graft removal (1).[13] Of the 9 recipients from Sweden, reported recipient complications were pleural effusion (2), anemia secondary to a retroperitoneal hematoma requiring blood transfusion (1), uterine graft infection requiring removal (1), graft thrombosis (1), and rejection (5 episodes).[12] Other reported recipient complications include vaginal cuff hemorrhage and candida vasculitis in one patient requiring graft hysterectomy (1), lower respiratory tract infection (1), and pyelonephritis during pregnancy (1).[6] No recipient or donor deaths have been reported worldwide.

What is the risk of immunosuppression to the UTx recipient and child?

Immunosuppression for UTx is based on practices for other solid organs, particularly kidneys, and maintenance immunosuppression is typically CNI based. UTx differs from other solid organ transplants in that exposure to immunosuppression is time limited and the patients who undergo UTx are healthy at

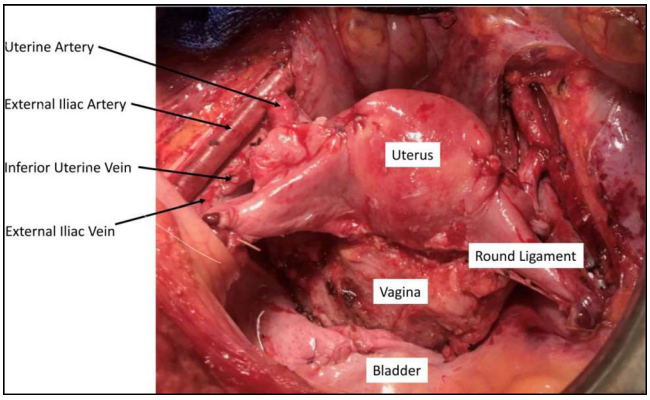

Figure 2. Uterus graft in situ after reperfusion and vaginal anastomosis. The uterine vessels are anastomosed bilaterally to the external iliac vessels. The round ligaments are suspended to the pelvic side wall.

baseline. The BUMC research protocol limits recipient-graft time to 5 years or two pregnancies, whichever comes first.[18] In addition, the graft may be removed after one pregnancy if the ongoing risk of maintaining the transplant is significant (e.g., acute kidney injury or preeclampsia during pregnancy).

The risks of immunosuppression to the UTx recipient are similar to the risks incurred by other solid organ transplant recipients: increased susceptibility to infections, side effects of medications such as CNI-related renal toxicity, posttransplant lymphoproliferative disease, and the potential long-term risk of cancer. The long-term outcomes for UTx recipients are currently unknown and need to be closely followed to determine the long-term risks of immunosuppression in this population.

From the standpoint of immunosuppression during pregnancy, while few UTx births have been reported to date, the safety of certain immunosuppression medications during pregnancy has been demonstrated in other solid organ transplant recipients.[19] The recommended maintenance immunosuppression in renal transplant recipients is CNI, azathioprine, and low-dose prednisone, and it is considered safe. Sirolimus and mycophenolate mofetil should be stopped 6 weeks prior to conception and should not be used during pregnancy. These same recommendations have been applied to UTx recipients.

The pregnancy-related complications of 9 UTx recipients that have been reported include preeclampsia, obstetric cholestasis, preterm prelabor rupture of membranes, and subchorionic hematoma.[2–4,6,20,21] In these 9 recipients, no neonatal complications were reported. The neonatal outcomes of 7 pregnancies reported from the BUMC trial are as follows: the median gestational age was 36 weeks and 6 days, the median APGAR score at 5 minutes was 9, and all babies had an appropriate birth weight for gestational age.[18] It is essential that UTx programs report pregnancy-related complications and neonatal complications and that these complications are included in registries for UTx.

What are the possible justifications for the risks of a non–lifesaving transplant?

While UTx is not a lifesaving transplant, its purpose is to improve quality of life in women with AUFI who desire to

carry their own pregnancies. It addresses a previously untreatable form of infertility. And, infertility is defined as a disease by the World Health Organization, associated with negative social and psychological sequela, affecting around 6% of couples in the US.[22,23] Treatment of infertility with assistive reproductive therapies, mainly in vitro fertilization (IVF), is generally accepted as mainstream medical practice and is valued because it gives couples the option to have their own child.

UTx is a type of assistive reproductive therapy that includes IVF but has additional risks associated with immunosuppressive medication, multiple surgical procedures, and high-risk pregnancy. The justification of UTx depends on the perceived value or benefit of UTx vs the risks and harms associated with it. To date, there are few reports on the value of UTx, as defined by recipients. A case series of two UTx recipients who had experienced pregnancy found that they felt that UTx was incredibly valuable and, if given the option, they would choose to undergo UTx again.[11] Semistructured interviews of the 9 UTx recipients from the first trial in Sweden identified a feeling of being a woman like everybody else and a chance of hope for pregnancy and motherhood as valuable aspects of UTx.[24] All participants in this study, regardless of outcome, were pleased that they had attempted to achieve motherhood through UTx. While these studies provide some limited insight into the value and justification of UTx, more research is needed to study the impact of UTx on recipients' quality of life, aiming to understand if their experiences with UTx, pregnancy, childbirth, and motherhood ultimately provide the desired value and are worth the risks in their own calculations. Moreover, the experiences of UTx recipients who experience graft failures or graft losses or are unable to achieve pregnancy are equally essential in the analysis of the benefits, value, risks, and harms of UTx.

What is the expected cost of the procedure? Is it likely to be covered by insurance? Are complications from the procedure or the cost of the birth covered by insurance?

To date, UTx has only been performed within research trials in the United States and has, therefore, been paid for by research funding. Recently, the US Uterus Transplant Consortium successfully worked with the American Medical Association to develop current procedural terminology (CPT) codes for UTx and related procedures, which is a positive step toward transitioning UTx to a clinical procedure.[25] It is very challenging to predict the exact cost of UTx because it encompasses IVF, donor surgery (either living or deceased), recipient UTx surgery, immunosuppression, embryo transfer, pregnancy, cesarean section, and graft hysterectomy. The time on immunosuppression, number of embryo transfers, number of pregnancies, and number of surgeries all affect the cost of UTx, so the cost will vary widely among UTx recipients based on these factors.

What we can predict is that UTx is not likely to be fully covered by insurance in the US. UTx intersects the areas of infertility treatment and vascular composite allotransplantation (VCA), neither of which is widely covered by insurance in the US. Therefore, IVF, donor and recipient operations, embryo transfer, and immunosuppression medication costs will most likely be out-of-pocket for UTx recipients. It is also difficult to predict if and what complications related to UTx will be covered by insurance. However, maternity and newborn care are considered essential benefits for insurance in the US, and we expect that this aspect of UTx will be covered, as it is with IVF.

How should the community address the disparity in access if only private-pay patients can afford the procedure?

This is a question for the treatment of infertility and VCA transplantation in general. From the perspective of infertility, we have to treat this condition as a disease rather than a mere inconvenience. Infertility has a psychological impact similar to that of cancer, cardiac rehabilitation, and hypertension.[26] Second, we have to treat infertility interventions as medical interventions that address a serious disease. If we have social buy-in to the concept that infertility is a disease and that treatment should be covered by insurance in general, then we can address the particular need of patients with AUFI to have the option to undergo UTx covered by insurance.

Similarly, VCA transplantation is considered a quality-of-life rather than lifesaving transplantation. While insurance companies typically cover the costs related to lifesaving organ transplantation and subsequent immunosuppression management, they have not been willing to cover the more established VCA procedures such as face and upper-extremity transplant. As with infertility treatments, insurance coverage of other VCA organs may need to be achieved to set the standard for insurance coverage of UTx.

CONCLUSIONS

UTx has been shown to be technically feasible, reproducible, and successful in terms of achieving the ultimate goal of healthy live births. UTx is a unique intersection between transplantation and reproductive health and has the potential to improve the lives of women with AUFI who desire to carry their own pregnancies. While many unknowns remain related to risks, benefits, value, cost, and insurance coverage, none of these barriers is insurmountable, and we see a bright future for the field of UTx.

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